REMARKS

Claims 15-21 and 23-27 are pending. Claims 15-25 are rejected. Claims 26-27 are new. Claim 15 is amended in light of the Examiner's rejection based on US 5,389,382 with support for said amendment found at page 6 lines 34-36 and page 10, lines 1-2. Claim 19 is amended in light of the instant Specification. Claim 22 is canceled. No new matter has been added.

Rejection under 35 USC § 112 ¶2

Claim 19 is rejected as indefinite for allegedly failing to provide antecedent basis for the term "polymeric polypeptides." Claim 19 has been amended to provide antecedent basis for the aforementioned term. In light of the changes, the Examiner's reasons for the rejection should no longer apply.

Rejection under 35 USC § 103

Claims 15-25 are rejected for allegedly being obvious in light of US 5,389,382.

To establish *prima facie* obviousness, the examiner must show in the prior art some suggestion or motivation to make the claimed invention, a reasonable expectation for success in doing so, and a teaching or suggestion of each claim element (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ 2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)).

The Examiner has not made the required showing.

The Examiner argues, in regards to US 5,389,382, that it would have been reasonable to modify the process of said cited art using conventional continuous processing and mixing means. In response, Applicants again point out that the batchwise operation disclosed by US 5,389,382 has to be followed by a filtration step to separate any coarse particles. (*see* examples 1 and 2 of the cited art.). The extra step of filtration requirement provides proof to show that the teaching in US 5,389,382 would not lead one of ordinary skill in the art to proceed with the process of said cited art to obtain particles possessing uniform size. The instant invention claims uniform nanoparticulates and the Examiner is directed to amended Claim 15 and new Claim 26 wherein said claims recite

uniform size limitations. Support for amended Claim 15 can be found on page 10, lines 1-2, of the instant Specification.

Moreover, one of ordinary skill in the art at the time of filing would not have expected that preparations containing acrylate based polymers in the core would give particularly stable nanodispersions such as disclosed in the instant invention. Dr. Bernd Liepold has provided comparative data relating to the preparations as disclosed by US 5,389,382 (*see* attached Declaration under 37 CFR 1.132 on a separate sheet). Employing Lopinavir, a protease inhibitor structurally related to the active ingredient of US 5,389,382, Dr. Liepold has demonstrated further that the major portion of the resulting product did not show particles sizes in the claimed range (*see* page of 3 the attached declaration). The resultant particles were primarily in the range of 20 μm. Some nano-sized particles between 1 and less than 5 μm did form but one of ordinary skill in the art would disregard the process for producing said particles since a yield rate of 3.6% is not acceptable.

The nano-sized core/shell particles of the instant invention, containing an acrylate based polymer such as Kollicoat ™, are particularly stable in regards to particle size (*see* Example 1 of the instant invention). Also, contrary to the cited art, there is no need for removal of extraneous coarse material prior to the determination of particle size in the instant invention.

Moreover, after spray-drying and re-dispersion in water, nanoparticulate dispersions with stable particle size are formed. Dispersions obtained without an acrylate based polymer such as Kollicoat ™ have increased particle size. In light of the teaching of US 5,389,382, one of ordinary skill in the art would not expect to achieve these results.

For at least the reasons expressed above, it is urged that the prior art references cited by the examiner either singly or in combination fail to anticipate or suggest the present invention as defined by the Claims. Accordingly, a *prima facie* case of obviousness has not been established by the Examiner, and the rejection under 35 USC § 103 should be withdrawn.

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re Application of
Robert HEGER et al.
Serial No.09/857,480
Filed: July 12, 1999
For: NANOPARTICULATE CORE/SHELL SYSTEMS AND THE USE THEREOF IN PHARMACEUTICAL AND COSMETIC PREPARATIONS

D E C L A R A T I O N

I, Dr. Bernd Liepold, a citizen of Germany and a resident of Max-Reger-Strasse 22, 69121 Heidelberg, Germany, hereby declare and say as follows:

I am a fully trained chemist, having studied chemistry at the University of Erlangen in the period of from 1987 to 1993.

I was awarded my PhD in chemistry at Friedrich Alexander University, Erlangen, where in the period of from 1993 to 1996 I worked on structure elucidation and synthesis of bioactive compounds .

I joined an affiliate company of BASF Aktiengesellschaft, located in Ludwigshafen, Germany, in 1997, where I have been engaged in research and development in the field of pharmaceutical formulations.

I have carefully studied the Office Actions of August 24, 2004 and of May 5, 2005, and the rejection of the claims under 35 U.S.C. § 103 (a) based on the teaching of List et al. (US 5,389,382) which document I have studied as well.

Now, hereby, I want to state the following:

According to List et al. hydrosols with a particle size between 1 nanometer and 1 micrometer are obtained by a process comprising that a solution of an active ingredient in an organic solvent miscible with water is mixed with water under conditions that a colloid, insoluble in water, is present in the organic solvent and a water soluble colloid is present in the water (cf. Col. 6, lines 11).

According to example 4 of List et al. a solution of 1 g ethyl cellulose N7 and 0.4 g of the active ingredient progesterone in 40 ml of 94% ethanol is rapidly poured into a vigorously stirred solution of 4.0 g gelatin in 200 ml water. The mixture is then treated as described in Example 1. According to Example 1 any coarse particles are separated by filtration through a paper filter with a pore size of 5 µm. The resulting particles are described as having an average diameter of 0.245 µm.

Example 4 of List et al. (US 5,389,382) was repeated. Since neither the active ingredient Progesterone used according to Example 4 of List et al. nor any of the other actives mentioned in this document were not available and could not be obtained with a reasonable amount of effort, another active ingredient with an equally low solubility in water was chosen.

The chosen active was Lopinavir, a compound comparable to Ritonavir used in Example 1 of the present patent application both in structure and low solubility in water.

Thus, a solution of 1 g ethyl cellulose N7 and 0.4 g Lopinavir in 40 ml of 94 % ethanol was rapidly added to a solution of 4 g gelatin in 200 ml water under vigorous stirring with an Ultra-Turrax T25 to give a cloudy dispersion with considerable amounts of clotted material.

The dispersion was not filtered, but analysed in total for particle size immediately after preparation of the dispersion. The determination of particle size as volume weighted mean was carried out with a Mastersizer.

When evaluating the results of the particle size measurements it should be kept in mind that according to the said Example 4 of List et al the dispersion was filtered through a 5µm filter prior to measurement of particle size in order to remove coarse particles. No disclosure regarding the amount of coarse particles thus removed or the yield of nanoparticles can be found in either of the examples.

The analysis of the particle size of the dispersion obtained in the manner described above gave the following results:

The average particle size of the total of the particles was 20.6 µm. 7.6 % b.w., based on the total of the particles, showed a particle size < 5 µm. Based on the total amount of particles 4 % b.w. showed a particle size between 1 and < 5 µm and only 3.6 % b.w. of the particles were found to have a particle size < 1 µm.
The remaining portion of the particles, i.e. 92.4 % b.w., were found to have an average particle size of < 5 µm and up to more than 20 µm.

Even though in principle nanosized particles, i.e. particles with a size < 1 µm, can be obtained in minor amounts according to the process disclosed by List et al., an expert skilled in the art desirous of finding a method to produce nanosized particles would not be motivated by a prior art method yielding only such minor amounts.

The presently claimed nanosized core/shell particles wherein the core contains an acrylate based polymer, e.g. Kollicoat® MAE, are particularly stable with regard to particle size as is shown for instance in Example 1 of the application. The examples do not mention the necessity to remove coarse material prior to determination of particle size.

Even after spry-drying the dispersion and re-dispersion in water stable nanoparticulate systems are obtained. Dispersion obtained without Kollicoat tend to increase in particle size. In my view this was not to be expected in view of the teaching of List et al..

I further declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so are made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Ludwigshafen, Germany, this 25th day of November, 2005.

B. Zimmermann

Signature of Declarant